

1. A method for treating a patient diagnosed as having a lower than normal HDL-cholesterol level, a higher than normal triglyceride level, or a cardiovascular disease, said method comprising administering to said patient a compound that modulates LXR-mediated transcriptional activity.

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2. The method of claim 1, wherein said compound is an oxysterol.

3. The method of claim 1, wherein said compound is selected from the group consisting of 24-(S),25-epoxycholesterol; 24(S)-hydroxycholesterol;
10 22-(R)-hydroxycholesterol; 24(R),25-epoxycholesterol;
22(R)-hydroxy-24(S),25-epoxycholesterol;
22(S)-hydroxy-24(R),25-epoxycholesterol; 24-(S),25-iminocholesterol;
methyl-38-hydroxycholesterol; N,N-dimethyl-3 β -hydroxycholesterol;
24(R)-hydroxycholesterol; 22(S)-hydroxycholesterol;
15 22(R),24(S)-dihydroxycholesterol; 25-hydroxycholesterol;
22(R)-hydroxycholesterol; 22(S)-hydroxycholesterol;
24(S),25-dihydroxycholesterol; 24(R),25-dihydroxycholesterol;
24,25-dehydrocholesterol; 25-epoxy-22(R)-hydroxycholesterol;
20(S)-hydroxycholesterol; (20R,22R)-cholest-5-ene-3 β ,20,22-triol;
20 4,4-dimethyl-5- α -cholesta-8,14,24-trien-3- β -ol;
7 α -hydroxy-24(S),25-epoxycholesterol; 7 β -hydroxy-24(S),25-epoxycholesterol;
7-oxo-24(S),25-epoxycholesterol; 7 α -hydroxycholesterol; 7-oxocholesterol;
and desmosterol.

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4. The method of claim 1, wherein said LXR is LXR α .

5. A method for treating a patient diagnosed as having a lower than normal HDL-cholesterol level, a higher than normal triglyceride level, or a cardiovascular disease, said method comprising administering to said patient a compound that modulates RXR-mediated transcriptional activity.

6. The method of claim 5, wherein said RXR is RXR α .

7. A method for determining whether a candidate compound modulates ABC1 expression, said method comprising the steps of:

(a) providing a nucleic acid molecule comprising an ABC1 regulatory region or promoter linked to a reporter gene;

(b) contacting said nucleic acid molecule with said candidate compound; and

(c) measuring expression of said reporter gene, wherein altered reporter gene expression, relative to said reporter gene expression of a corresponding control nucleic acid molecule not contacted with said compound, indicates that said candidate compound modulates ABC1 expression.

8. The method of claim 7, wherein said regulatory region comprises 50 consecutive nucleotides selected from nucleotides 5854 to 6694, 7756 to 8318, 10479 to 10825, 15214 to 16068, 21636 to 22111, 27898 to 28721, 32951 to 33743, 36065 to 36847, 39730 to 40577, 4543 to 5287, and 45081 to 55639 of SEQ ID NO: 1.

9. The method of claim 7, wherein said regulatory region comprises a binding site for a transcription factor selected from a group consisting of LXRs, RXRs, RORs, SREBPs, and PPARs.

5 10. A substantially pure nucleic acid molecule comprising a region that is substantially identical to at least fifty contiguous nucleotides of nucleotides 5854 to 6694, 7756 to 8318, 10479 to 10825, 15214 to 16068, 21636 to 22111, 27898 to 28721, 32951 to 33743, 36065 to 36847, 39730 to 40577, 4543 to 5287, or 45081 to 55639 of SEQ ID NO: 1.

10 11. A substantially pure nucleic acid molecule comprising a region that is substantially identical to nucleotides 1 to 28,707 of SEQ ID NO: 1.

15 12. A substantially pure nucleic acid molecule comprising a region that is substantially identical to nucleotides 29,011 to 53,228 of SEQ ID NO: 1.

13. A cell expressing the nucleic acid molecule of claim 10.

20 14. A non-human mammal expressing the nucleic acid molecule of claim 10.

15. A method of treating a human having a higher than normal triglyceride level, said method comprising administering to said human an ABC1 polypeptide, or triglyceride-regulating fragment thereof.

25 16. The method of claim 15, wherein said ABC1 polypeptide has the

sequence of SEQ ID NO: 5.

17. The method of claim 15, wherein said ABC1 polypeptide comprises a R⇒K mutation at position 219 or a V⇒A mutation at position 399.

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18. The method of claim 15, wherein said ABC1 polypeptide comprises a mutation that increases its stability.

19. The method of claim 15, wherein said ABC1 polypeptide comprises a mutation that increases its biological activity.

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20. A method of treating a human having a higher than normal triglyceride level, said method comprising administering to said human a nucleic acid molecule encoding an ABC1 polypeptide or a triglyceride-regulating fragment thereof.

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21. The method of claim 20, wherein said ABC1 polypeptide has the amino acid sequence of SEQ ID NO: 5.

22. The method of claim 20, wherein said ABC1 polypeptide comprises a R⇒K mutation at position 219 or a V⇒A mutation at position 399.

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23. The method of claim 20, wherein said ABC1 polypeptide comprises a mutation that increases its stability.

24. The method of claim 20, wherein said ABC1 polypeptide comprises a mutation that increases its biological activity.

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25. The method of claim 20, wherein said biological activity is regulation of cholesterol.

26. The method of claim 20, wherein said human has a lower than normal HDL-cholesterol level.

27. A method of treating a human having a higher than normal triglyceride level, said method comprising administering to said human a compound that increases ABC1 biological activity or that mimics the activity of wild-type ABC1, R219K ABC1, or V399A ABC1.

28. A non-human mammal comprising a transgene comprising a nucleic acid molecule encoding a dominant-negative ABC1 polypeptide, said dominant-negative polypeptide comprising a M \Rightarrow T mutation at position 1091.

29. A method for determining whether a candidate compound decreases the inhibition of a dominant-negative ABC1 polypeptide, said dominant-negative polypeptide comprising a M \Rightarrow T mutation at position 1091, said method comprising the steps of:

- (a) providing a cell expressing a dominant-negative ABC1 polypeptide;
- (b) contacting said cell with said candidate compound; and
- (c) measuring ABC1 biological activity of said cell,

wherein an increase in said ABC1 biological activity, relative to said ABC1 biological activity in a corresponding control cell not contacted with said compound, indicates that said candidate compound decreases the inhibition of a dominant-negative ABC1 polypeptide.

30. A method for predicting a person's response to a triglyceride-lowering drug, comprising determining whether the person has a polymorphism in an ABC1 gene, promoter, or regulatory sequence that alters the person's response to said drug.

31. A method for determining whether a candidate compound is useful for modulating triglyceride levels, said method comprising the steps of:

- (a) providing a chicken comprising a mutation in an *ABC1* gene;
 - (b) administering said candidate compound to said chicken; and
 - (c) measuring ABC1 biological activity in said chicken,
- wherein altered ABC1 biological activity, relative to said ABC1 biological activity in a corresponding control chicken not contacted with said compound, indicates that said candidate compound is useful for modulating triglyceride levels.

32. The method of claim 31, wherein said ABC1 biological activity is transport of cholesterol.

33. A method for determining whether a candidate compound is useful for modulating triglyceride levels, said method comprising the steps of:

- (a) providing a cell expressing an ABC1 polypeptide comprising amino acids 1 to 60 of SEQ ID NO: 5;
 - (b) contacting said cell with said candidate compound; and
 - (c) measuring ABC1 biological activity of said cell,
- wherein altered ABC1 biological activity, relative to said ABC1 biological activity in a corresponding control cell not contacted with said compound, indicates that said candidate compound is useful for modulating triglyceride levels.

34. A method for determining whether a candidate compound is useful for modulating triglyceride levels, said method comprising the steps of:

- (a) providing a cell expressing an *ABC1* gene or a fragment thereof;
- (b) contacting said cell with said candidate compound; and
- (c) measuring ABC1 expression of said cell,

wherein altered ABC1 expression, relative to said ABC1 expression in a corresponding control cell not contacted with said candidate compound, indicates that said candidate compound is useful for modulating triglyceride levels.

35. A method for determining whether a candidate compound is useful for modulating triglyceride levels, said method comprising the steps of:

(a) providing an ABC1 polypeptide comprising amino acids 1 to 60 of SEQ ID NO: 1;

(b) contacting said polypeptide with said candidate compound; and

(c) measuring ABC1 biological activity, wherein a change in ABC1 biological activity, relative to said ABC1 biological activity of a corresponding control ABC1 polypeptide not contacted with said compound, indicates that said candidate compound is useful for modulating triglyceride levels.

36. A method for determining whether a candidate compound is useful for modulating triglyceride levels, said method comprising the steps of:

(a) providing an ABC1 polypeptide comprising amino acids 1 to 60 of SEQ ID NO: 5;

(b) contacting said polypeptide with said candidate compound; and

(c) measuring expression of said ABC1 polypeptide, wherein a change in expression of said ABC1 polypeptide, relative to said

expression of a corresponding control ABC1 polypeptide not contacted with said compound, indicates that said candidate compound is useful for modulating triglyceride levels.

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37. A method for determining whether candidate compound is useful for modulating triglyceride levels, said method comprising the steps of:

(a) providing an ABC1 polypeptide comprising amino acids 1 to 60 of SEQ ID NO: 5;

(b) contacting said polypeptide with said candidate compound; and

10 (c) measuring binding of said ABC1 polypeptide to said candidate compound, wherein binding of said ABC1 polypeptide to said compound indicates that said candidate compound is useful for modulating triglyceride levels.

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38. A method for determining whether candidate compound is useful for modulating triglyceride levels, said method comprising the steps of:

(a) providing (i) an ABC1 polypeptide comprising amino acids 1 to 60 of SEQ ID NO: 5, and (ii) a second polypeptide that interacts with said ABC1 polypeptide;

(b) contacting said polypeptides with said candidate compound; and

20 (c) measuring interaction of said ABC1 polypeptide with said second polypeptide, wherein an alteration in the interaction of said ABC1 polypeptide with said second polypeptide indicates that said candidate compound is useful for modulating triglyceride levels.

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39. A method for determining whether a candidate compound is useful for modulating triglyceride levels, said method comprising the steps of:

(a) providing a cell comprising an ABC1 polypeptide comprising amino acids 1 to 60 of SEQ ID NO: 5;

(b) contacting said cell with said candidate compound; and

(c) measuring the half-life of said ABC1 polypeptide,

5 wherein an increase in said half-life, relative to said half-life in a corresponding control cell not contacted with said compound, indicates that said candidate compound is useful for modulating triglyceride levels.

40. A method for determining whether a candidate compound is useful for modulating triglyceride levels, said method comprising the steps of:

(a) providing an ABC1 polypeptide in a lipid membrane;

(b) contacting said polypeptide with said candidate compound; and

(c) measuring ABC1-mediated lipid transport across said lipid membrane,

10 wherein a change in lipid transport, relative to said lipid transport of a corresponding control ABC1 polypeptide not contacted with said compound, indicates that said candidate compound is useful for modulating triglyceride levels.

41. The method of claim 35-38, or 40, wherein said ABC1 polypeptide is in a cell-free system.

20 42. The method of claim 35-38, or 40, wherein said ABC1 polypeptide is in a cell.

43. The method of claim 42, wherein said cell is from a WHAM chicken.

25 44. The method of claim 42, wherein said cell is in a human or in a non-

human mammal.

45. The method of claim 44, wherein said animal is a WHAM chicken.

5 46. The method of claim 31, 33, or 35, wherein said biological activity is transport of lipid or interleukin-1.

47. The method of claim 46, wherein said lipid is cholesterol.

10 48. The method of claim 47, wherein said cholesterol is HDL-cholesterol.

49. The method of claim 31, 33, or 35, wherein said biological activity is binding or hydrolysis of ATP by the ABC1 polypeptide.

15 ✓ 50. A method of determining a propensity for a disease or condition in a subject, wherein said disease or condition is selected from the group consisting of a lower than normal HDL level, a higher than normal triglyceride level, and a cardiovascular disease, said method comprising determining the presence or absence of at least one ABC1 polymorphism in the polynucleotide sequence of an ABC1 regulatory region, promoter, or coding sequence or in the amino acid sequence of an ABC1 protein in a sample obtained from said subject, wherein the presence or absence of said ABC1 polymorphism is indicative of a risk for said disease or condition.

20 51. The method of claim 50, further comprising analyzing at least five ABC1 polymorphic sites in said polynucleotide sequence or said amino acid

sequence,

52. A method for determining whether an ABC1 polymorphism is indicative of a risk for a disease or condition in a subject, wherein said disease or condition is selected from the group consisting of a lower than normal HDL level, a higher than normal triglyceride level, and a cardiovascular disease, said method comprising the steps of:

(a) determining whether the prevalence of said disease or condition in a first subject or set of subjects differs from said prevalence of said disease or condition in a second subject or set of subjects;

(b) analyzing the polynucleotide sequence of an ABC1 regulatory region, promoter, or coding sequence or the amino acid sequence of an ABC1 protein in a sample obtained from said first subject or set of subjects and said second subject or set of subjects; and

(c) determining whether at least one ABC1 polymorphism differs between said first subject or set of subjects and said second subject or set of subjects, wherein the presence or absence of said ABC1 polymorphism is correlated with said prevalence of said disease or condition, thereby determining whether said ABC1 polymorphism is indicative of said risk.

53. The method of claim 52, further comprising analyzing at least five ABC1 polymorphic sites in said polynucleotide sequence or said amino acid sequence.

54. An electronic database comprising a plurality of sequence records of ABC1 polymorphisms correlated to records of predisposition to or prevalence of a disease or condition selected from the group consisting of a lower than normal

HDL cholesterol level, a higher than normal triglyceride level, and a cardiovascular disease.

55. A method for selecting a preferred therapy for modulating ABC1 activity or expression in a subject, said method comprising:

(a) determining the presence or absence of at least one ABC1 polymorphism in the polynucleotide sequence of an ABC1 regulatory region, promoter, or coding sequence or in the amino acid sequence of an ABC1 protein in a sample obtained from said subject, wherein the presence or absence of said ABC1 polymorphism is indicative of the safety or efficacy of at least one therapy for modulating ABC1 expression or activity; and

(b) determining a preferred therapy for modulating ABC1 expression or activity in said subject.

56. The method of claim 55, further comprising analyzing at least five ABC1 polymorphic sites in said polynucleotide sequence or said amino acid sequence.

57. A method for determining whether a candidate compound is useful for the treatment of a disease or condition selected from the group consisting of a lower than normal HDL cholesterol level, a higher than normal triglyceride level, and a cardiovascular disease; said method comprising the steps of:

(a) providing an assay system having a measurable ABC1 biological activity;

(b) contacting said assay system with said candidate compound; and

(c) measuring ABC1 biological activity or ABC1 phosphorylation, wherein modulation of ABC1 biological activity or ABC1 phosphorylation,

relative to said ABC1 biological activity or ABC1 phosphorylation in a corresponding control assay system not contacted with said candidate compound, indicates that said candidate compound is useful for the treatment of said disease or condition.

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58. The method of claim 57, wherein said assay system is a cell based system

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59. The method of claim 57, wherein said assay system is a cell free system.

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60. A method for identifying a compound to be tested for an ability to ameliorate a disease or condition selected from the group consisting of a lower than normal HDL cholesterol level, a higher than normal triglyceride level, and a cardiovascular disease, said method comprising the steps of:

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(a) contacting a subject or cell with a candidate compound;
(b) measuring ABC1 expression, activity, or protein phosphorylation in said subject or cell; wherein altered ABC1 expression, activity, or protein phosphorylation; relative to said ABC1 expression, activity, or protein phosphorylation in a corresponding control subject or cell not contacted with said candidate compound; identifies said candidate compound as a compound to be tested for an ability to ameliorate said disease or condition.

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61. The method of claim 57 or 60, wherein said candidate compound modulates said ABC1 protein phosphorylation and said ABC1 activity.

62. A method for determining whether a candidate compound is useful for

modulating a disease or condition selected from the group consisting of a lower than normal HDL cholesterol level, a higher than normal triglyceride level, and a cardiovascular disease, said method comprising the steps of:

- (a) providing a cell expressing an ABC1 gene or a fragment thereof;
- (b) contacting said cell with said candidate compound; and
- (c) measuring ABC1 activity of said cell, wherein altered ABC1 activity, relative to said ABC1 activity in a corresponding control cell not contacted with said compound, indicates that said candidate compound is useful for modulating said disease or condition.

63. A method for determining whether a candidate compound is useful for modulating a disease or condition selected from the group consisting of a lower than normal HDL cholesterol level, a higher than normal triglyceride level, and a cardiovascular disease, said method comprising the steps of:

- (a) contacting a cell expressing an ABC1 protein with said candidate compound;
- (b) measuring the phosphorylation of said ABC1 protein; wherein altered ABC1 protein phosphorylation, relative to said ABC1 protein phosphorylation in a corresponding control cell not contacted with said candidate compound, indicates that said is useful for modulating said disease or condition.

64. A compound useful for the treatment of a disease or condition selected from the group consisting of a lower than normal HDL cholesterol level, a higher than normal triglyceride level, and a cardiovascular disease, wherein said compound modulates ABC1 biological activity, and wherein said compound is identified by the steps of:

- (a) providing an assay system having a measurable ABC1 biological

activity;

(b) contacting said assay system with said compound; and

(c) measuring ABC1 biological activity, wherein modulation of ABC1 biological activity, relative to said ABC1 biological activity in a corresponding control assay system not contacted with said compound, indicates that said compound is useful for the treatment of said disease or condition.

65. A compound useful for the treatment of a disease or condition selected from the group consisting of a lower than normal HDL cholesterol level, a higher than normal triglyceride level, and a cardiovascular disease, wherein said compound induces a change in ABC1 biological activity that mimics the change in ABC1 biological activity induced by the R219K ABC1 mutation.

66. A compound useful for the treatment of a disease or condition selected from the group consisting of a lower than normal HDL cholesterol level, a higher than normal triglyceride level, and a cardiovascular disease, wherein said compound binds or interacts with residue R219 of ABC1, thereby mimicking the change in ABC1 activity induced by the R219K ABC1 mutation.

67. A compound useful for the treatment of a disease or condition selected from the group consisting of a lower than normal HDL cholesterol level, a higher than normal triglyceride level, and a cardiovascular disease, wherein said compound induces a change in ABC1 biological activity that mimics the change in ABC1 biological activity induced by the V339A ABC1 mutation.

68. A compound useful for the treatment of a disease or condition selected from the group consisting of a lower than normal HDL cholesterol level, a higher

than normal triglyceride level, and a cardiovascular disease, wherein said compound binds or interacts with residue V399 of ABC1, thereby mimicking the change in ABC1 activity induced by the V399A ABC1 mutation.

5 69. A compound that modulates ABC1 activity and binds or interacts with an amino acid of ABC1, wherein said amino acid is a residue selected from amino acids 119 to 319 of ABC1 (SEQ ID NO: 5) or amino acids 299 to 499 of ABC1 (SEQ ID NO: 5).

10 70. A method for determining whether a candidate compound is useful for the treatment a disease or condition selected from the group consisting of a lower than normal HDL cholesterol level, a higher than normal triglyceride level, and a cardiovascular disease, said method comprising the steps of:

15 (a) providing an assay system having a measurable LXR biological activity;
 (b) contacting the assay system with said candidate compound; and
 (c) measuring LXR biological activity, wherein modulation of LXR biological activity, relative to said LXR biological activity in a corresponding control assay system not contacted with said candidate compound, indicates that said candidate compound is useful for the treatment of said disease or condition.

20 71. A method for determining whether a candidate compound is useful for modulating ABC1 biological activity, said method comprising the steps of:

25 (a) providing an assay system having a measurable LXR biological activity;
 (b) contacting said assay system with said candidate compound; and
 (c) measuring LXR biological activity, wherein modulation of LXR biological activity, relative to said LXR biological activity in a corresponding control assay system not contacted with said candidate compound, indicates that

said candidate compound is useful for modulating ABC1 biological activity.

72. The method of claim 71, wherein said LXR biological activity is modulation of ABC1 expression.

5 73. A method for identifying a compound to be tested for an ability to modulate ABC1 biological activity, said method comprising the steps of:

- (a) contacting a subject or cell with a candidate compound;
- (b) assaying the activity of the LXR gene product in said subject or cell;

10 wherein modulation of said activity, relative to said activity in a corresponding control subject or cell not contacted with said candidate compound, identifies said candidate compound as a compound to be tested for an ability to modulate the biological activity of ABC1.

15 74. Use of an LXR gene product in an assay to identify compounds useful for the treatment of a disease or condition selected from the group consisting of a lower than normal HDL cholesterol level, a higher than normal triglyceride level, and a cardiovascular disease.

20 75. Use of a compound that modulates the activity or expression of an LXR gene product for the treatment of a disease or condition selected from the group consisting of a lower than normal HDL cholesterol level, a higher than normal triglyceride level, and a cardiovascular disease.

25 76. A method for identifying a compound to be tested for an ability to treat a disease or condition selected from the group consisting of a lower than normal HDL cholesterol level, a higher than normal triglyceride level, and a

cardiovascular disease, said method comprising the steps of:

- (a) providing an assay system having a measurable LXR biological activity;
- (b) contacting said assay system with the candidate compound; and
- (c) measuring LXR biological activity, wherein modulation of said LXR

biological activity, relative to said LXR biological activity in a corresponding control assay system not contacted with said candidate compound, identifies said candidate compound as a compound to be tested for an ability to treat said disease or condition.

77. A method for screening an candidate LXR agonist for the ability to treat a disease or condition selected from the group consisting of a lower than normal HDL cholesterol level, a higher than normal triglyceride level, and a cardiovascular disease, said method comprising the steps of:

- (a) contacting said a with said candidate LXR agonist; and
- (b) measuring cholesterol efflux activity of said cell, wherein an increase in said cholesterol efflux activity in said cell, relative to said cholesterol efflux in a corresponding control cell not contacted with said candidate LXR agonist, indicates that said candidate LXR agonist is useful for treating said disease or condition.

78. A method for screening a candidate LXR modulating compound for the ability to treat a disease or condition selected from the group consisting of a lower than normal HDL cholesterol level, a higher than normal triglyceride level, and a cardiovascular disease, said method comprising the steps of:

- (a) contacting a cell with said candidate LXR modulating compound; and
- (b) measuring ABC1 biological activity of said cell; wherein an increase in ABC1 biological activity in said cell, relative to said ABC1 biological activity in a

corresponding control cell not contacted with said LXR modulating compound,
indicates that said LXR modulating compound is useful for treating said disease or
condition.

5 79. The method of any one of claims 71-78, wherein said cell or assay
system comprises an exogenously supplied copy of an LXRE selected from the
group consisting of SEQ ID NO: 94, SEQ ID NO: 92, and the LXRE consensus
motif at nucleotide -7670 of the 3' end of intron 1.

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